REMARKS

Applicant respectfully requests reconsideration of the present application in view of the reasons that follow.

Claims 17-33 and 43-56, previously withdrawn as being drawn to non-elected subject matter, are canceled without prejudice to presenting claims to the same or similar subject matter in a related, divisional or continuation application. After entrance of the present amendment, claims 1-16, 34-42 and 57 are pending.

35 U.S.C. § 112, first paragraph (enablement)

Claims 1-16, 34-42 and 57 stand rejected under 35 U.S.C. § 112, as failing to comply with the enablement requirement. The Examiner explicitly acknowledges that the specification is "enabling for some compounds such as drawn specifically to the treatment for certain catechol-containing compounds and their prodrugs , which selectively reduce blood flow to a tumor region," but asserts that the application "does not reasonably provide enablement for ZSB-71 for the selective reduction of blood flow to a tumor region." Applicant appreciates the Examiner's acknowledgement of a general level of enablement. Applicant calls the Examiner's attention to example 4, which explicitly demonstrates a 46.7% decrease in blood flow in a mouse tumor system by the compound ZSB-71 (pages 67-68, especially Table 2).

As the Examiner notes, many factors, including the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided, the existence of working examples and the quantity of experimentation, must be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement. In the present application, each of these factors supports a conclusion that the claimed invention is fully supported by the specification.

Nature of the Invention, Breadth of the claims and State of the art

The nature of the invention is a composition that can selectively reduce blood flow to a tumor region and for a reactive oxygen species *in vivo* and which comprises a an anticancer agent having a quinone, quinone prodrug, catechol or catechol prodrug moiety.

The Examiner identifies US Patent Publication 2003-1292233A1, to Warthow et al., as representing the prior art and disclosing categories and classes of neoplastic agents that read on each and every limitation of claim 3. Applicant disagrees with this characterization. Warthow et al., provides an extended discussion about cancer therapeutics in general and various targeting mechanisms, but this reference is not relevant to selective reduction in blood flow to a tumor region or formation of reactive oxygen species *in vivo*, by quinone- or catechol-containing compounds. Other than a general acknowledgement of tubulin-binding agents as a class of anti-cancer agents (see page 14, first paragraph, first column), this reference specifies none of the limitations of claim 3. While Applicant disagrees with the particular reference identified by the Examiner, Applicant submits that the state of the art is well developed, as evidenced by the references cited in Applicant's Information Disclosure Statement, submitted 3 June 2004.

Amount of direction or Guidance provided and Working examples

The Examiner asserts that the amount of direction and guidance with regard to ZSB-71 is deficient because "actual description, explanation and/or reasoning as to how ZSB-71 is used in order to arrive at the treatment limitations of the claims are ***completely silent***." (Emphasis added). Applicant strongly disagrees.

Notably, the specification explicitly teaches that ZSB-71 is cytotoxic to tumor cells, with an IC_{50} of 0.887 μM, as demonstrated by MTT assay (Example 4 and Table 2, column 3). Applicant submits that this result, alone, demonstrates the utility of the presently claimed composition as an anticancer agent. The same example, further, demonstrates

that ZSB-71 reduces blood flow in an *in vivo* tumor system. Administration of ZSB-71 to tumor-bearing mice causes a 46.7% reduction in functional blood vessels in the tumor, as measured by accessibility of the blood vessels to 0.1 μm fluorescently labeled beads. Notably, every compound of the invention that was tested demonstrated tubulin-binding activity, toxicity to tumor cells and substantial decreases in tumor blood flow *in vivo*.

Additionally, the specification (paragraph bridging pages 20 and 21) teaches that

> *ROS are directly cytotoxic to tumor cells because they react directly to form adducts with cell components including protein, lipid, and DNA. Alternatively, they can initiate the formation of lipid hydroperoxides which in turn act as mutagens by covalently modifying DNA. Hydroxyl anion radicals, for example, are some of the most powerful oxidants in biological systems and can mediate many destructive mechanisms on tumor cells, including membrane damage, lipid peroxidation, and depolyrnerization of macromolecules.*

This passage provides an explanation and reasoning for using compounds capable of forming a reactive oxygen species to treat cancer. Page 25 provides a further explanation of the advantages of combining tumor blood flow decrease with the cytotoxicity of a reactive oxygen species. Thus the specification is far from "silent" regarding actual description, explanation and/or reasoning as to how ZSB-71 can be used successfully by one of ordinary skill in the art without undue experimentation.

Predictability and Quantity of experimentation necessary

The Examiner cites a thesis by Smita Chawla in support of the proposition that the presently claimed subject matter is unpredictable. In particular, the Examiner calls attention to statements made at page 80 of this thesis, including "the rapid oxidation of catechols generates reactive quinones that can irritate the skin." As discussed in detail at pages 19-21 of the specification, the present invention depends upon the formation of quinones from the corresponding catechol. The quinone then induces oxidative stress in the tumor cells either directly or by formation of reactive oxygen species, such as a semi-quinone radical ion. Thus rapid formation of a quinine would not interfere with function of the present invention. Additionally, because the present invention functions by decreasing blood flow in tumors, direct application of these compounds to the skin is

unlikely. Regardless, in the event that such compositions interact with skin, Applicant submits that skin irritation would be insignificant in comparison to the life-saving activity against cancer.

The Examiner also points to the statement that "the catechol structure…**may** behave as a chelator to the copper ions of tyrosinase" and to a discussion of how such structures may interact with tyrosinase. First Applicant notes that these statements are speculative. Second, these speculations must be balanced against the actual results presented in the specification of the present application. These actual results demonstrate that ZSB-71 and related compounds are cytotoxic to tumor cells and reduce blood flow to tumors *in vivo*. Any amount of chelation of the copper of tyrosinase that **may** have occurred did not interfere with the expected vascular disrupting activity of the compounds.

The Examiner further asserts that the quantity of experimentation necessary would be undue because of the absence of embodiments drawn to a method process of use in a human patient. Applicant submits that the present claims are not limited to use only in human patients and, further, that an *in vivo* model is provided at pages 67-75. Thus the specification provides actual evidence of successful treatment and Applicant submits that it would require nothing more than ordinary experimentation to extend these results to other animals, including humans.

In response to the Examiner's assertion that "[a] method of administration in the claims is not established," Applicant submits that such an administration method is not necessary to the composition claim. One of ordinary skill in the art could ascertain an appropriate administration method as a standard step in development of a therapy. Further, the specification provides proof that at least intraperitoneal injection (example 4, page 68, and example 6, page 73) is sufficient.

Finally, the Examiner raises a concern regarding a target population. As the claims are limited to a composition which selectively reduces blood flow to a tumor region, it

reasonably follows that the target population would be one that has a tumor region in which blood flow could be reduced. Applicant submits that those of ordinary skill in the art would have no difficulty identifying appropriate subjects for the claimed composition. Matching patients with appropriate therapies is standard practice in medicine and would require nothing more than standard actions by one of ordinary skill in the art.

Thus the balance of the evidence indicates that the present invention is predictable and that nothing more than reasonable experimentation would be necessary to make and use the compositions of the claims. Accordingly, Applicant submits that the present claims are fully enabled and requests withdrawal of the present rejection.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-4279. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-4279. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-4279.

Respectfully submitted,

By:

Date 2 April 2009

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